UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,670	09/30/2005	Werner Mederski	MERCK-3070	5551

23599 7590 07/09/2008

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
BIANCHI, KRISTIN A	

ART UNIT	PAPER NUMBER
1626	

NOTIFICATION DATE	DELIVERY MODE
07/09/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Office Action Summary	Application No.	Applicant(s)	
	10/551,670	MEDERSKI ET AL.	
	Examiner	Art Unit	
	KRISTIN BIANCHI	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *18-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/30/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-20 are pending in the instant application. Claims 18-20 are withdrawn pursuant to 37 CFR 1.142(b) as being drawn to non-elected subject matter. Claims 1-17 are rejected.

Priority

This application claims benefit of PCT/EP04/02405 filed on March 9, 2004 and foreign priority (Germany) documents: 10334174.9 filed on July 26, 2003, 10334174.0 filed on July 26, 2003, 10329457.0 filed on July 1, 2003, 10329295.0 filed on June 30, 2003, 10327428.6 filed on June 18, 2003, and 10315377.2 filed on April 3, 2003. English translations of all the aforementioned documents have not been submitted in this application.

Information Disclosure Statement

Applicant's information disclosure statement filed on September 30, 2005 has been considered. A signed copy of form 1449 is submitted herewith.

Election/Restrictions

Applicant's election with traverse of Group I and the species1-[(4-chlor-phenyl)]-2-{[4-(3-oxo-morpholin- 4-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine- 1,2-dicarboxamide in the reply filed on May 15, 2008 is acknowledged. The traversal is on the ground(s): "The traversal is on the basis that the PTO has not established that it would pose an undue burden to examine the full scope of the application."

This is not found persuasive. The search for the product as claimed (i.e. compounds of the formula IV) is not coextensive with the search for the process of making the product.

For example, in regards to the instant election (i.e. the process of making compounds of the formula I), a separate search would be required to determine the totality of the prior art that may exist that anticipates and/or makes obvious the claimed compounds of formula IV.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1-17 contain or depend on a claim which contains the phrase "pharmaceutically usable derivatives" without defining exactly what the meets and bounds of 'derivatives' is. Applicant's recite on pages 6 and 15 of the specification: "The term pharmaceutically usable derivatives is taken to mean, for example, the salts of the compounds according to the invention and also so-called prodrug compounds." This language is not limiting nor defining the scope of the invention and therefore does not teach one of skill in the art how to make and use all possible 'derivatives' of the compounds: there is an infinite number of 'derivatives'.

This rejection can be overcome by deleting the term "pharmaceutically usable derivatives" or replacing this term with a more descriptive term such as "pharmaceutically acceptable salts".

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the preparation of compounds of formula I and stereoisomers thereof, does not reasonably provide enablement for the preparation of solvates thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with the claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

The nature of the invention

The nature of the invention is a process for the preparation of compounds of the formula I and pharmaceutically usable derivatives, **solvates** and stereoisomers thereof, including mixtures thereof in all ratios.

The state of the prior art/level of ordinary skill/level of predictability

Active pharmaceutical ingredients are frequently delivered to the patient in the solid-state as part of an approved dosage form (e.g., tablets, capsules, etc.). Solids

provide a convenient, compact, and generally stable format to store an active pharmaceutical ingredient or a drug product. Understanding and controlling the solid-state chemistry of active pharmaceutical ingredients, both as pure drug substances and in formulated products, is therefore an important aspect of the drug development process. Active pharmaceutical ingredients can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals, and amorphous solids. Each form displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability, and other performance characteristics of the drug. Hence, it is critical to understand the relationship between the particular solid form of a compound and its functional properties.

For ionizable compounds, preparation of salt forms using pharmaceutically acceptable acids and bases is a common strategy to improve bioavailability. However, the preparation of other solid forms such as polymorphs and solvates are not so common to be predictable. In order to obtain patent protection on these forms, some of which may have significantly different properties and relevance as development candidates, it is essential to prepare them, identify conditions for making them, and evaluate their properties as valuable new pharmaceutical materials. Therefore, for these reasons, the state of the prior art is one of unpredictability.

As stated above, crystalline solids can exist in the form of polymorph, solvates or hydrates. "Phase transitions such as polymorph interconversion, desolvation of solvate, formation of hydrate, and conversion of crystalline to amorphous form may occur during various pharmaceutical processes, which may alter the dissolution rate

and transport characteristics of the drug. Hence, it is desirable to choose the most suitable and stable form of the drug in the initial stages of drug development" (Vippagunta *et al.*, abstract). In further discussing the predictability of the formation of solvates, Vippagunta *et al.* discloses that "predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds" (page 18, section 3.4).

The amount of direction or guidance present/existence of working examples

A disclosure should contain representative examples which provide reasonable assurance to one skilled in the art that the compounds which fall within the scope of a claim will posses the alleged activity. There is no data present in the specification for the preparation of solvates of the compounds of formula I. The specification discloses (page 15) "The term solvates of the compounds is taken to mean adducts of inert solvent molecules onto the compounds which form owing to their mutual attractive force. Solvates are, for example, mono- or dehydrates or alcoholates." The specification does not, however, disclose any working examples for the preparation of solvates of the compounds of formula I.

Breadth of the claims

The instant breadth of the rejected claims is broader than the disclosure, specifically; the instant claims include any solvates of the compounds of formula I.

The quantity of experimentation needed

While the level of skill in the pharmaceutical arts is high, it would require undue experimentation for one of ordinary skill in the pertinent art to prepare *any* solvate of the compounds of formula I.

The science of crystallization has evolved such that, without guidance or working examples in the specification, the claim lacks enablement. This rejection can be overcome by deletion of the word "solvate" from the claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KRISTIN BIANCHI whose telephone number is (571)270-5232. The examiner can normally be reached on Mon-Fri 7am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kamal A Saeed, Ph.D./
Primary Examiner, Art Unit 1626

Kristin Bianchi
Examiner
Art Unit 1626

***